Development of and future prospects for pyrethroid chemistry†

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Abstract: The pyrethroid group of insecticides consists of natural pyrethrins derived from pyrethrum flowers and synthetic derivatives which are similar in chemical structure to the natural compounds. Pyrethroids have been considered to be ideal insecticides because of their rapid knock-down effect against insects in a minimal dose and low mammalian toxicity.

Keywords: natural pyrethrins; synthetic pyrethroids; fish toxicity; pyrethroid resistance; chrysanthemic acid esters; chrysanthemum acid esters

1 INTRODUCTION

Studies on pyrethroid chemistry started about 1910, and have since involved two main periods each of approximately the same duration. The first period was devoted to the elucidation of the chemical structure of natural pyrethrins, which consists of an acid moiety, an ester linkage and an alcohol moiety, and resulted in discoveries of the six active ingredients, pyrethrins-I and -II, cinerins-I and -II and jasmolins-I and -II. In 1958, the absolute configuration of the alcohol moiety was determined and the whole structure was then available for the natural pyrethrins. During the next period, a number of useful synthetic pyrethroids were invented, based on knowledge gained during the first period. Endowed with advantageous properties over the natural pyrethrins, such as enhanced insecticidal activity, improved photostability and lower cost, some of synthetic pyrethroids were put into practical use in broad areas including household insecticides and agrochemicals. The demand for synthetic pyrethroids is still expanding as substitutes for natural pyrethrins. High toxicity to fish and development of pyrethroid resistance in some pests are cited as common shortcomings for these compounds. One theme in the coming third period of research will likely concern the solution of these problems. Silafluofen, a non-ester pyrethroid-like compound with low toxicity to fish, will provide one possible solution. Especially in coping with another cross-resistance problem, it will be helpful to come back to the whole structure of natural pyrethrins and to re-study the significance of the mixture composition of chrysanthemic acid esters with chrysanthemum acid esters.

2 PYRETHRUM FLOWERS AND THE CHEMICAL STUDY OF NATURAL PYRETHRINS (THE FIRST PERIOD)

2.1 Pyrethrum flowers

Pyrethrum flowers are of the genus *Chrysanthemum* and there are two kinds of species, those with white and those with red flowers. Only white flowers, those of *Chrysanthemum cinerariaefolium* Vis, contain the insecticidally active components, while those with red flowers are merely ornamental plants.

The original home of *C cinerariaefolium* is the Dalmatian region of former Yugoslavia, on the Mediterranean coast of the Adriatic Sea, east of Italy. It is said that pyrethrum was discovered in 1694 but inhabitants of the pyrethrum-growing region seem to have discovered the particular efficacy of this plant earlier and to have used it in powder form for insecticide applications. The verification of its insecticidal activity was made in 1840.

It was not until 1860 that pyrethrum flowers were introduced to the USA and pyrethrum was introduced into Japan in 1885. Pyrethrum flowers of German origin were brought to the Medical Herb Garden in Meguro, Tokyo. Another record reveals the fact that pyrethrum flowers from an American source were grown in the test farm of the Agricultural College in Komaba, Tokyo.

E Ueyama was the first man to promote cultivation of pyrethrum in Wakayama prefecture. He was the first president of Dainihon Jochugiku Co.

Thereafter pyrethrum cultivation was spread around the country, and the export of dried flowers from Japan began in 1898. Forty years later (1938),

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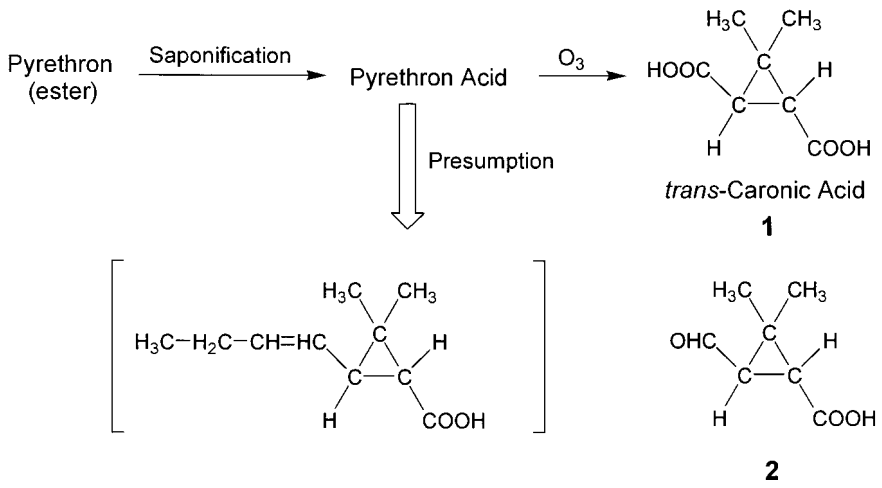


Figure 1. Isolation of *trans*-caronic acid.

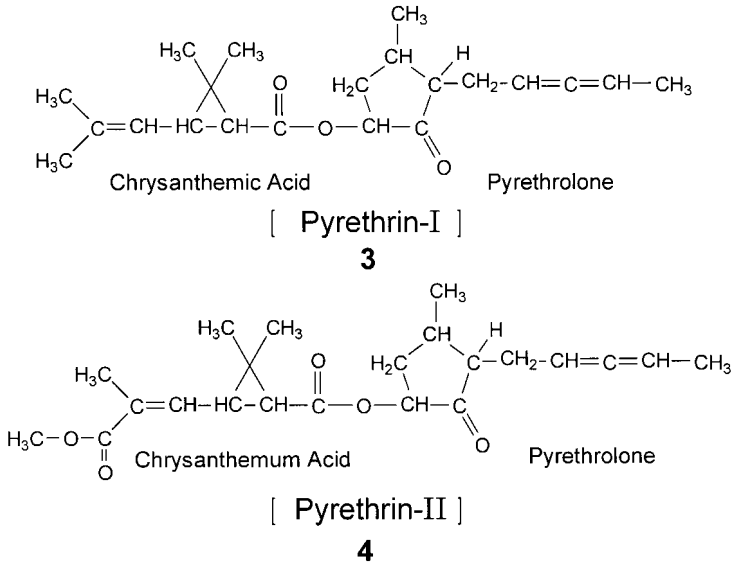


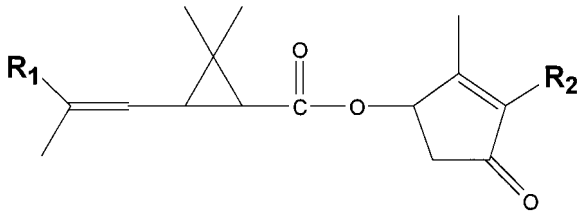
Figure 2. Proposed chemical structures.

Japanese pyrethrum production reached a peak of 13 000 tons per year in terms of dry flowers, which was about 70% of the world's production at that time. After World War II cultivation of pyrethrum in Japan was greatly reduced because food was more acutely needed, and then declined to only 1000 tons in 1965. Kenya and Tanzania overtook Japan as the main producers owing to the suitable climate for cultivation and the national promotion programs. At present African countries including Kenya, Tanzania and Rwanda produce the great majority of the world's pyrethrum, and other producers are Tasmania and Papua New Guinea.

2.2 Chemical study of natural pyrethrins

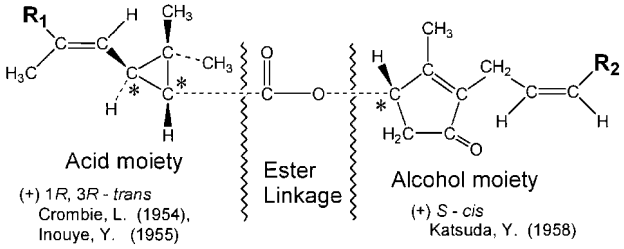
Fujitani[1] separated the insecticidally active syrupy ester from pyrethrum flowers and called the ester 'pyrethron'. Yamamoto[2,3] subjected the hydrolysis product of this pyrethron to ozone oxidation, and isolated *trans*-caronic acid and aldehyde (**1** and **2**, respectively, Fig 1). Although Yamamoto did not determine the structure of this acid (**1**), he presumed it to be 'pyrethron acid'.

At any rate, he first confirmed the existence of the cyclopropane ring structure in the molecule of natural pyrethrins in 1923. The next year, Staudinger and Ruzicka[4] proposed the structures **3** and **4** (Fig 2) for pyrethrins-I and -II from natural pyrethrins. Although there were some errors in the light of our present knowledge, their studies certainly represented an outstanding achievement. In 1945, LaForge and Barthel[5] reported that natural pyrethrins consisted of four homologues, pyrethrins-I and -II, and cinerins-I and -II (**5, 6, 7** and **8**, Figs 3 and 4), and determined their planar structures as shown in Fig 3. It was made clear later that natural pyrethrins contain six components, pyrethrins-I, -II, cinerins-I, -II, and jasmolins-I, -II (**9** and **10**, Fig 4) and that these are ester compounds formed from acid and alcohol moieties. The absolute configuration of the acid moiety was determined by Crombie and Harper[6] and by Inouye, Takeshita and Ohno[7] in 1954 and 1955, respectively.



Compound	Acid (R_1)	Alcohol (R_2)	
5 Pyrethrin I	Chrysanthemic Acid	$-CH_2-CH=CH-CH=CH_2$	Pyrethrolone
6 Pyrethrin II	Chrysanthemum Acid	$-CH_2-CH=CH-CH=CH_2$	Pyrethrolone
7 Cinerin I	Chrysanthemic Acid	$-CH_2-CH=CH-CH_3$	Cinerolone
8 Cinerin II	Chrysanthemum Acid	$-CH_2-CH=CH-CH_3$	Cinerolone

Figure 3. Correction of chemical structures.



Compound	R_1	R_2	%
5 Pyrethrin I	$-CH_3$	$-CH=CH_2$	38
6 Pyrethrin II	$-COOCH_3$	$-CH=CH_2$	30
7 Cinerin I	$-CH_3$	$-CH_3$	9
8 Cinerin II	$-COOCH_3$	$-CH_3$	13
9 Jasmolin I	$-CH_3$	$-CH_2CH_3$	5
10 Jasmolin II	$-COOCH_3$	$-CH_2CH_3$	5

Figure 4. Absolute configuration of natural pyrethrins.

In 1958, the present author determined the absolute configuration of the alcohol moiety.[8]

The complete elucidation of the stereochemistry of natural pyrethrins formed a model for the development of various kinds of synthetic compounds. Natural pyrethrins and synthetic derivatives are all called pyrethroids.

3 DEVELOPMENT OF SYNTHETIC PYRETHROIDS (THE SECOND PERIOD)

3.1 Modification of the alcohol moiety

Figure 5 shows the development of various synthetic pyrethroids invented by retaining chrysanthemic acid as the acid moiety and modifying the alcohol moiety. Many useful compounds were derived from the structural modification of natural pyrethrin-I (**5**). Those compounds underlined[9–16] have been commercially produced and have been in broad use as active ingredients, mainly for household insecticides.

The present author's group studied the alcohol moiety apart from the cyclopentenolone ring. With emphasis on the benzyl ring structure, we contributed a paper in 1965 on the insecticidally active compound 'benathrin' (**12**) to *Bochu-kagaku* of Kyoto University.[17] Elliott *et al*[18] also reported the same series of compounds, including 2,6-dimethyl-4-allylbenzyl chrysanthemate, in the same year. After that, our studies focused on furan ring compounds,[19] leading to the invention of the pyrethroids japothrin (**13**) and furamethrin (**14**)[11] in 1966. Elliott *et al*[12] investigated the same furan ring compounds and developed resmethrin (**15**) in 1966.

In the 1960s, pyrethroid research on the alcohol moiety in pyrethroids resulted in significant developments in Japan, the UK, and the USA so that natural pyrethrins were replaced by synthetic pyrethroids, mainly in the area of household insecticides.

3.2 Modification of the acid moiety and ester linkage

As shown in Fig 6 many pyrethroids having a chemically stable phenoxybenzyl group as the alcohol moiety but a modified acid moiety were invented. Pyrethroids such as permethrin **(17)**[20] and fenvalerate **(18)**[21] have been used for agricultural purposes because of their chemical stability. Studies on this modification in the 1970s were conducted by agrochemical companies around the world. At present pyrethroids account for about 20% of the total volume of insecticides used all over the world.

Figure 7 shows compounds obtained by replacing the ester linkage with other linkages, examples being etofenprox **(19)**[22] and silafluofen **(20)**.[23] Developed mainly in the 1980s, these compounds are quite different in structure from the prototype pyrethrins, and do not fall into the classical pyrethroid type of insecticides. Silafluofen, which we invented, is featured by the possession of a silicon atom in the molecule. It is certain, however, that the idea of this compound emerged in the course of pyrethroid development. We were amazed that silafluofen was

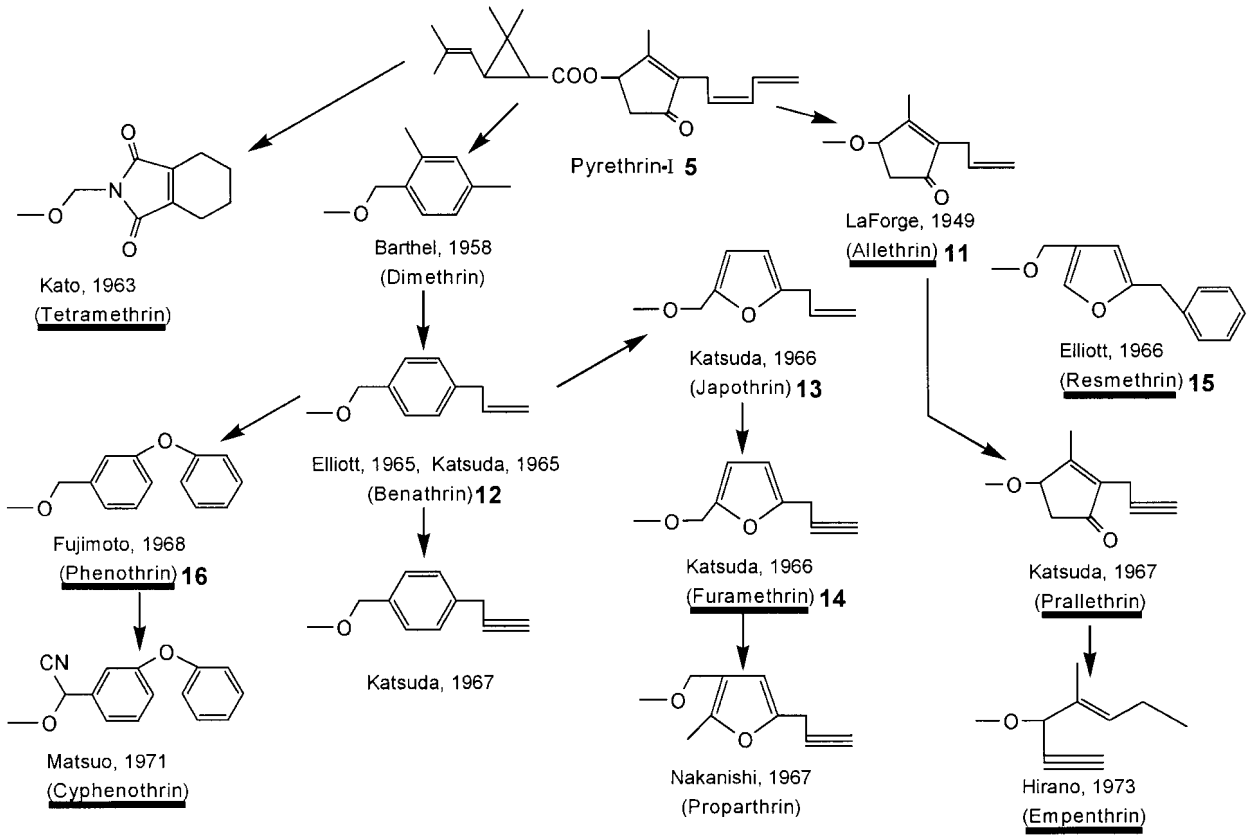


Figure 5. Modification of alcohol moiety (Dates are cited in terms of patent application).

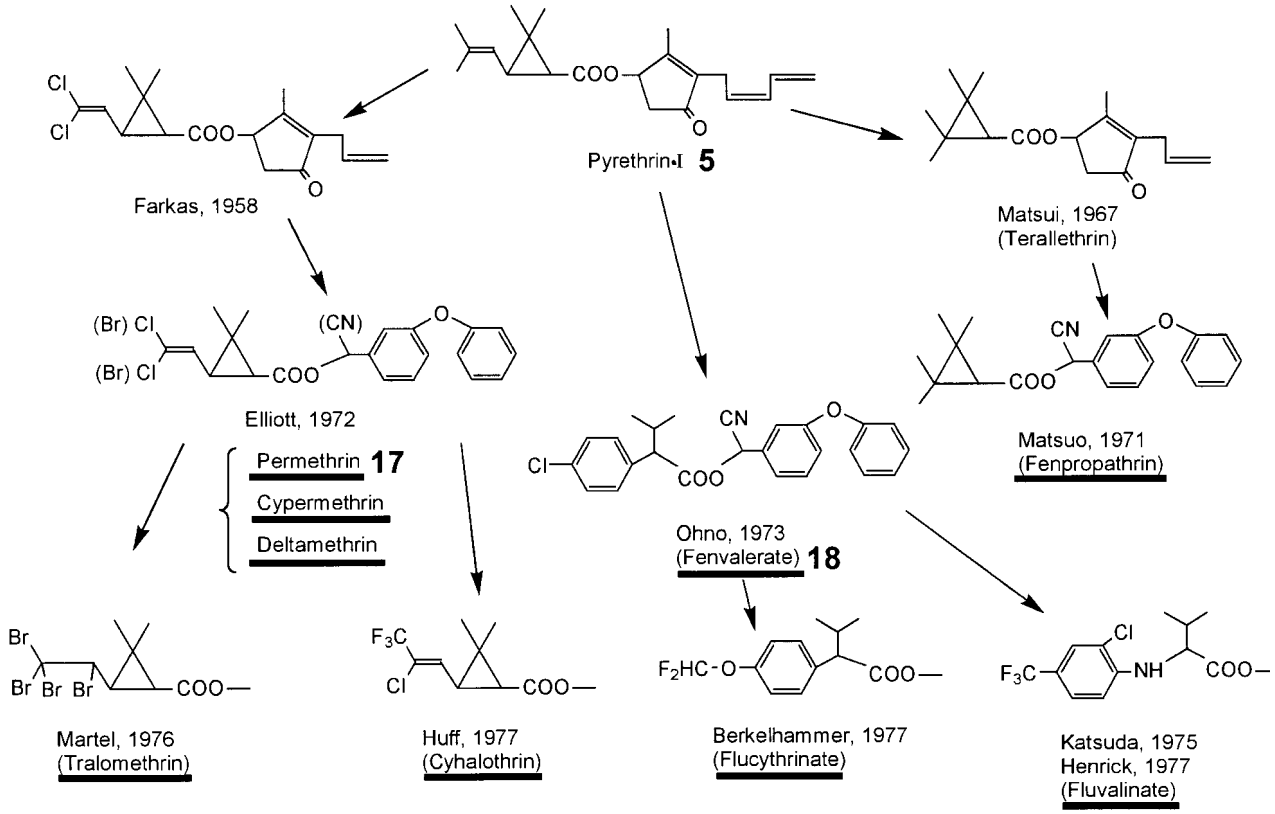


Figure 6. Modification of acid moiety (Dates are cited in terms of patent application).

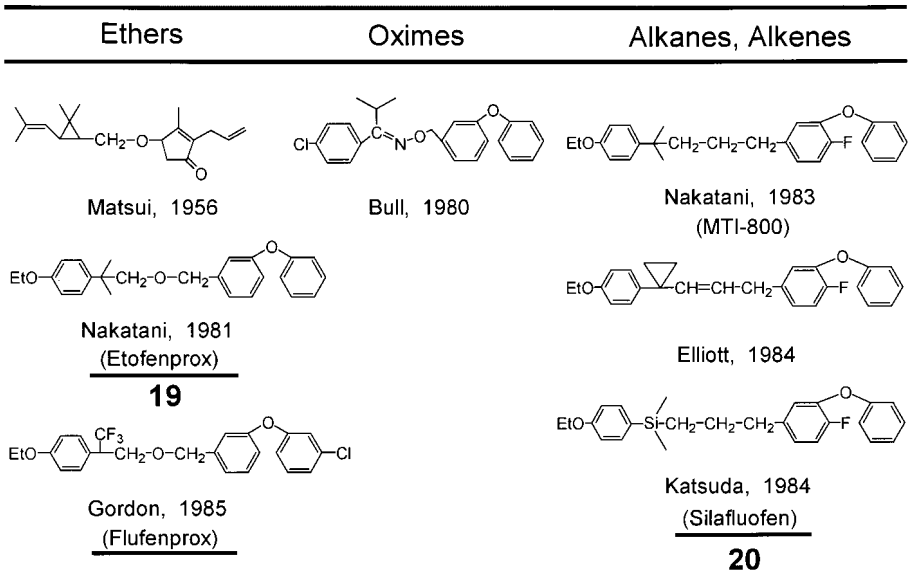


Figure 7. Modification of linkage moiety (Dates are cited in terms of patent application).

Table 1. Selective toxicity of insecticides

	LD_{50} ($mg\,kg^{-1}$)			
Insecticide	*Mammal (rat)*[a]	*Insect*[a]	*Ratio of selectivity*	*Mode of action*
Carbamate	45 (15)	2.8 (27)	16	Inhibition of acetylcholinesterase
Organophosphorus compound	67 (83)	2.0 (50)	33	Inhibition of acetylcholinesterase
Organochlorine compound	230 (21)	2.6 (26)	91	Action on the nervous system
Pyrethroid	2000 (11)	0.45 (35)	4500	Action on the nervous system

[a] Number of insecticides tested in parentheses.

publicized almost simultaneously from different countries.[23–26]

3.3 Biological activity characteristics of pyrethroids

Pyrethroids show the following characteristics:

(1) Quick knock-down effect against insects;
(2) Low mammalian toxicity;
(3) Efficacy against insects with organophosphorus- and/or carbamate-resistant strains;
(4) Easy decomposition in the environment.

Such characteristics make pyrethroids useful for household insecticides, and those with improved chemical stability, for example, to light and in the air, are valuable agrochemicals.

Concerning (1) and (2), the data in Table 1 indicate the selective toxicity of some classes insecticide.[27] For example, the average LD_{50} value for 15 carbamates for rats is $45\,mg\,kg^{-1}$, whereas that for 27 carbamates for insects is $2.8\,mg\,kg^{-1}$. Accordingly, the ratio of LD_{50} values for mammals and insects is 16, which is an index of the selective toxicity. The corresponding ratio for organophosphorus compounds is 33, and that for organochlorine compounds is 91. In contrast, the ratio for pyrethroids is 4500, indicating much lower toxicity to mammals in spite of their excellent insecticidal activity.

One of the reasons for the favourable selective toxicity of pyrethroids is as follows: pyrethroids which act on the nervous system are metabolised and excreted by mammals before reaching the central nervous system. On the other hand, pyrethroids do reach the nervous system in insects, causing such symptoms as excitement and paralysis, eventually leading to knock-down or death of the insects.

As mentioned previously, a number of pyrethroids and pyrethroid-like compounds have been studied, developed and put into practical use since the 1950s. However, high fish toxicity and development of pyrethroid resistance in some pests are cited as common shortcomings for these compounds.

4 FUTURE RESEARCH THEMES TO BE SOLVED (THE THIRD PERIOD)

4.1 Fish toxicity

Because of high toxicity to fish, the use of pyrethroids has been greatly restricted in and around water systems, for example, in rooms with a water tank including pet fish, or in and around paddy fields and fishponds.

Table 2. Fish toxicity of pyrethroids

	Level of fish toxicity in Japan[a]			Actual value
		LC_{50} (mg litre^{-1})		LC_{50} (mg litre^{-1})
Pyrethroid	Class	Carp	Daphnid	Rainbow trout[b]
Silafluofen (**20**)	A	>10	>0.5	>1000
Etofenprox (**19**)	B	>10	<0.5	
		0.5∼10		0.28
Permethrin (**17**)				0.0025
Fenvalerate (**18**)	C	<0.5		0.0036
Deltamethrin				0.0009

[a] Classified on a scale A–C denoting increasing toxicity to fish as used in Japan.
[b] LC_{50} values (mg litre^{-1}, 96h) for rainbow trout from *The Pesticide Manual*, 11th edn, ed by Tomlin CDS, British Crop Protection Council, Farnham, UK (1997).

Silafluofen (**20**, Fig 7) will provide one possible solution toward this problem. Its combination of high insecticidal activity, low mammalian toxicity, high chemical stability (to light, in soil, to pH, etc), low fish toxicity and activity as a contact and stomach poison makes this compound quite different from conventional pyrethroids, especially in terms of the last two factors.

In Japan, fish toxicity is graded A–C (Table 2) and pyrethroids generally belong to class C due to their high toxicity to fish. In contrast silafluofen, with low toxicity to fish, is in class A, and its use as an insecticide in paddy fields has been increasing year by year in Japan. For example, the LC_{50} value of silafluofen for rainbow trout is >1000 mg litre^{-1}, whereas that of permethrin (**17**, Fig 6) is 2.5 μg litre^{-1} indicating a fish toxicity for silafluofen less than 2.5×10^{-6} times that of permethrin. The reason for silafluofen's low fish toxicity is unknown and studies on this mechanism would be an interesting topic in the search for pyrethroids with low fish toxicity.

4.2 Cross-resistance of pyrethroids

Using a topical application method, efficacy tests of some pyrethroids were conducted against the susceptible CSMA strain and the pyrethroid-resistant Hiroyama strain of *Musca domestica* L originally collected from a hog farm in Hiroyama, Niigata Prefecture. The LD_{50} values of permethrin (**17**, Fig 6) and phenothrin (**16**, Fig 5)[14] are shown in Table 3, and R/S ratios calculated from the values for these compounds are 204 and 283, respectively.

The Hiroyama strain showed high cross-resistance to all tested synthetic pyrethroids as well as to permethrin and phenothrin, whereas the R/S ratio for natural pyrethrins was only about 7 (Table 3). Moreover, the R/S ratio for racemic allethrin (**11**, Fig 5) was 97, indicating slow development of resistance compared with permethrin and phenothrin. These results are consistent with the data reported by Sawicki *et al*[28] at an ICPC meeting in Ottawa in 1986. These authors theorized that pyrethroids with the cyclopentenolone ring showed only a slight resistance.

Table 3. Pyrethroid resistance against *Musca domestica*

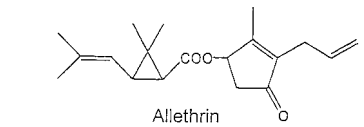
	LD_{50} (μg per female)[a]		
Compound	CSMA (S)[b]	Hiroyama (R)[c]	R/S ratio
Permethrin (**17**)	0.028	5.700	204
Phenothrin (**16**)	0.047	13.289	283
Natural pyrethrin[d]	0.784	5.384	7
Allethrin (racemic)[e]	0.417	40.355	97
Allethrin (bioallethrin)[f]	0.210	14.368	68
Allethrin (S-biol)[g]	0.081	2.721	33

[a] Topical application method, 0.5 μl injection.
[b] Susceptible strain of *M domestica*.
[c] Resistant strain of *M domestica*.
[d] Alcohol moiety; *d* form, and acid moiety; *d- trans* form.
[e] Alcohol moiety; *dl* form, and acid moiety; *dl- cis, trans* form.
[f] Alcohol moiety; *dl* form, and acid moiety; *d- trans* form.
[g] Alcohol moiety; *d* form, and acid moiety; *d- trans* form.

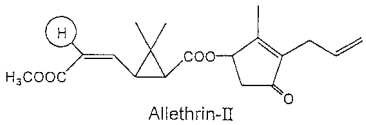
In the series of allethrin homologues, the R/S ratios for racemic, bioallethrin and S-biol were 97, 68 and 33, respectively. The closer the steric configuration of allethrin homologues comes to that of natural pyrethrins, the smaller the R/S ratio, that is, the level of resistance. However the R/S ratio for *d, d-trans* allethrin having the same steric configuration as natural pyrethrins is still greater than that of natural pyrethrins.

Except for the side-chain structure of the alcohol moiety, there is a big difference between natural pyrethrins and *d, d-trans* allethrin in that the former consist of the mixture of pyrethrins-I and -II (**5** and **6**, Fig 4), whereas the latter does not contain pyrethrin-II homologues.

Table 4. Chrysanthemic acid ester (Py-I) and modified chrysanthemum acid ester (Py-II)



Allethrin
11



Allethrin-II
21

	LD_{50} (μg per female)[a]		
Compound	CSMA (S)	Hiroyama (R)	R/S ratio
Allethrin (bioallethrin)	0.210	14.368	68
Allethrin- II	0.077	3.384	44
Allethrin/allethrin- II (1+1)	0.098 (0.144)[b]	3.870 (8.876)[b]	39

[a] Topical application method, 0.5 μl injection.
[b] Calculated based on values of allethrin and allethrin-II.

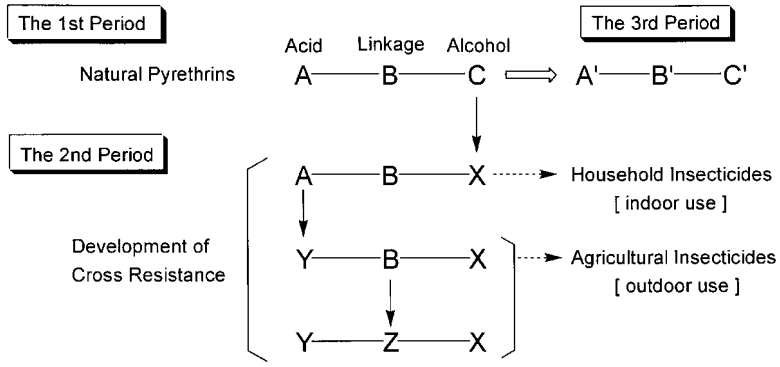


Figure 8. Development of and future prospects for pyrethroid chemistry.

Although pyrethrin-II (**4**, Fig 2) possesses a methyl group instead of a hydrogen atom as in allethrin, we prepared an ester of the modified chrysanthemum acid with allethrolone, that is, allethrin-II (**21**, Table 4). We then examined the LD_{50} values of allethrin (**11**, Table 4), allethrin-II (**21**, Table 4) and a $1+1$ mixture of allethrin and allethrin-II against CSMA and Hiroyama strains of *M domestica*. The test results, shown in Table 5, can be summarized as follows:

(1) Allethrin-II was more effective than allethrin against both susceptible (S) and resistant (R) strains of *M domestica;*
(2) The mixture of allethrin and allethrin-II showed a remarkable synergistic effect against both S and R strains of *M domestica;*
(3) R/S ratios decreased in the order of allethrin, allethrin-II and the mixture.

In splendid experiments with eight isomers of allethrin, Elliott proved in 1954 that the biological activity of compounds with the same planar structure can be greatly but systematically affected by steric configuration.[29] The present author still remembers having read the paper with great excitement at the age of 28.

5. CONCLUSION

My conclusion is summarized in Fig 8. The first period of research was devoted to the elucidation of the chemical structure of natural pyrethrins. In the figure [A-B-C], [A] shows acids of chrysanthemic acid and chrysanthemum acid, [B] represents the ester linkage, and [C] are alcohols of pyrethrolone, cinerolone and jasmolone.

The synthetic pyrethroid era of the second period began with studies on the replacement of the cyclopentenolone with other alcohol moieties, creating a number of compounds [A-B-X] for indoor household use. Subsequently, by replacing the cyclopropane ring with other acid functions, synthetic pyrethroids [Y-B-X] were developed for agrochemicals and outdoor use. Then the majority of research shifted to the modification of the ester linkage [Y-Z-X].

I assume that these partial structural modifications might be one of causes for the development of cross-resistance.

In the coming third period, the following should be kept in mind;

(1) learning from natural pyrethrins:
  (a) naturally occurring conformation;
  (b) existence of pyrethrin-II homologues;
(2) looking at the whole structure, not only a part.

I think it very important to consider the whole molecule structure [A′-B′-C′] in any future developments.

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